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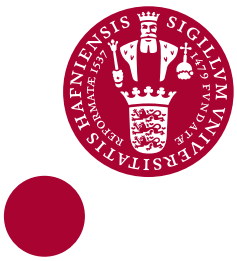

Oximes

unrecognized chameleons in general and specialized plant metabolism

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Oximes: Unrecognized Chameleons in General and Specialized Plant Metabolism

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This review is dedicated to the commemoration of Dr. Eric E. Conn who passed away on September 2nd, 2017. Intellect, eminent mentoring and kindness were the hallmarks of his life and basis for his numerous seminal scientific contributions to plant biochemistry

ABSTRACT

Oximes (R_1R_2C=NOH) are nitrogen-containing chemical constituents that are formed in species representing all kingdoms of life. In plants, oximes are positioned at important metabolic bifurcation points between general and specialized metabolism. The majority of plant oximes are amino acid-derived metabolites formed by the action of a cytochrome P450 from the CYP79 family. Auxin, cyanogenic glucosides, glucosinolates, and a number of other bioactive specialized metabolites including volatiles are produced from oximes. Oximes with the E configuration have high biological activity compared with Z-oximes. Oximes or their derivatives have been demonstrated or proposed to play roles in growth regulation, plant defense, pollinator attraction, and plant communication with the surrounding environment. In addition, oxime-derived products may serve as quenchers of reactive oxygen species and storage compounds for reduced nitrogen that may be released on demand by the activation of endogenous turnover pathways. As highly bioactive molecules, chemically synthesized oximes have found versatile uses in many sectors of society, especially in the agro- and medical sectors. This review provides an update on the structural diversity, occurrence, and biosynthesis of oximes in plants and discusses their role as key players in plant general and specialized metabolism.

Key words: structural diversity, CYP79, auxin, cyanogenic glucosides, volatile organic compounds, E-oxime, Z-oxime

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INTRODUCTION

Plant metabolites are commonly divided into general and specialized metabolites. Plant specialized metabolites (or bioactive natural products) are structurally and functionally extremely diverse, comprising more than 200 000 different compounds divided into different classes such as terpenoids, alkaloids, phenylpropanoids, cyanogenic glucosides, and glucosinolates. The occurrence of some specialized metabolites may be restricted to just a single plant species, whereas others are present in a specific or a few selected plant families. In contrast, general metabolites are widely distributed throughout the plant kingdom and are essential to plant growth and reproduction, e.g., hormones, carbohydrates, and amino acids.

Oximes (R_1R_2C=NOH) (Figure 1A) are an important compound class bridging general and specialized metabolism. Oximes have been known for more than 100 years (Donohue, 1956) with the first oxime, methylglyoxime (CH_3C(=NOH)CH(=NOH)) (Figure 1B), chemically synthesized in 1882 by the German chemists Victor Meyer and Alois Janny (Figure 2) (Meyer and Janny, 1882). During the 1960s, oximes were identified in plants as intermediates in the biosynthesis of the specialized metabolite classes cyanogenic glucosides (Tapper et al., 1967) and glucosinolates (formerly mustard oil glucosides) (Benn, 1965; Underhill, 1967) (Figure 1C and 1D). These classes of natural products have long been recognized as part of two-component defense systems against herbivores and pests, detonated by the action of specific β-glycosidases or thioglycosidases (myrosinases), resulting in release of a cyanide bomb

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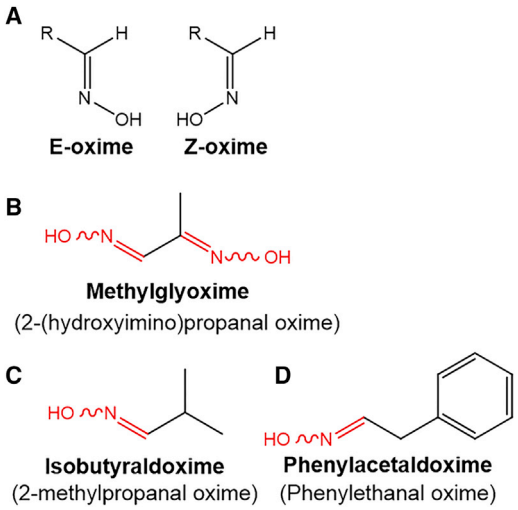


Figure 1. The Chemical Structure of an Oxime.
(A) Oximes may exist in two geometrical forms assigned either an E or a Z configuration.
(B) Methylglyoxime was chemically synthesized (Meyer and Janny, 1882).
(C and D) (C) Isobutyraldoxime from cyanogenic glucoside biosynthesis (Tapper et al., 1967) and **(D)** phenylacetaldoxime from glucosinolate biosynthesis (Underhill, 1967) were the first oximes identified in plants. The oxime function is marked in red.

or a mustard oil bomb, respectively (Morant et al., 2008). Both systems may provide resistance to generalist herbivores and pests including those attacking important crop plants and fruit trees (Patton et al., 1997; Gleadow and Woodrow, 2002; Ballhorn et al., 2005; Morant et al., 2008; Zagrobelny et al., 2008; Gleadow and Møller, 2014; Fang et al., 2016). It is now realized that cyanogenic glucosides and glucosinolates play many other roles in plants such as the fine-tuning of general metabolism (Møller, 2010; Neilson et al., 2013).

In plant general metabolism, oximes facilitate a range of processes important for plant growth and development. A key example is the important plant hormone auxin, first discovered in the 1930s (Mano and Nemoto, 2012). In addition, nitrogen fixation in leguminous plants is associated with the release of the oxime of oxaloacetate from root nodules and its further metabolism to release nitrite (Virtanen and Laine, 1939). Acetaldoxime (Table 1) has been identified as a product of nitrate reduction and assimilation in young leaves of soybean (*Glycine max*) (Mulvaney and Hageman, 1984; Van Den Boom et al., 2004). Further, oximes are formed by chemical reactions occurring in nature such as chemodenitrification reactions in soil organic matter (Thorn and Mikita, 2000). Oximes thus exist in both general and specialized plant metabolism either as end products or to be further converted to nitriles and a range of other metabolites. In many plant species the role and further metabolism of the oximes remain a mystery.

Naturally occurring oximes have been found to possess high biological activity. Likewise, chemically synthesized oximes are being used for a range of different purposes especially in the agro-sector. The occurrence of plant oximes was extensively reviewed by S. Mahadevan in 1973 (Mahadevan, 1973). Since then, no comprehensive review of oximes in plants has been published.

Figure 2. Portrait of Victor Meyer.
The German chemist Victor Meyer who, together with Alois Janny, reported the first chemically synthesized oxime. Unfortunately no picture of Alois Janny is available.

This is surprising considering the new knowledge gained on oxime prevalence, biosynthesis, and functionalities. Therefore, the purpose of this review is to provide an overview of these highlights, demonstrating the importance of oximes in general and specialized plant metabolism, stressing the need for more targeted studies on oximes in the future.

STRUCTURAL DIVERSITY OF OXIMES PRODUCED IN PLANTS

During the last 40 years, a number of structurally diverse oximes have been identified in plants (Table 1). As mentioned in the introduction, the first reports of oximes were published in 1967, identifying the presence of isobutyraldoxime and phenylacetaldoxime in linen flax (*Linum usitatissimum*) and garden nasturtium (*Tropaeolum majus*), respectively (Tapper et al., 1967; Underhill, 1967). These oximes are derived from the amino acids valine and phenylalanine. Since their identification in the 1960s, additional amino acid-derived oximes have been identified from isoleucine, leucine, methionine, tryptophan, and tyrosine (Table 1). The chemical structures are relatively simple, reflecting their parent amino acid, or with further modifications, for example, methylated oximes (oxime ethers) such as 2-methylbutanal *O*-methyloxime (Table 1). Structurally, the amino acid-derived oximes exist in two geometrical configurations, E and Z (Figure 1A). In many cases, the oxime configuration is not reported. In the cases where it is known, it proves important for their function (see details below).

To date such relatively simple oxime structures have been reported identified in approximately 45 different plant species (see Table 1), either as end products or as intermediates toward the formation of important specialized and general metabolites, including auxin, α-hydroxynitrile glucosides (cyanogenic glucosides), β- and γ-hydroxynitrile glucosides, glucosinolates, and camalexin.

Complex oximes, not obviously derived directly from amino acids, are rare in plants. To date, only three structures (Table 1) have been elucidated; citaldoxime was extracted from roots of sweet orange (*Citrus sinensis*) (Ito et al., 1990), canaline glyoxylate oxime was identified as a breakdown product of

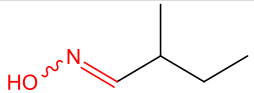
Oxime	Precursor	CYP79	Endpoint	Plant species	Reference
Aliphatic					
2-methylbutyraldoxime	Isoleucine	CYP79D1/ CYP79D2	Lotaustralin •	*Manihot esculenta*	(Andersen et al., 2000)
(2-methylbutanal oxime)		CYP79D3/ CYP79D4	Lotaustralin •, rhodiocyanoside A and D •	*Lotus japonicus*	(Forslund et al., 2004)
		CYP79D15	Lotaustralin •	*Trifolium repens*	(Olsen et al., 2008)
		CYP79D6v3/ CYP79D7v2	Herbivore induced •	*Populus trichocarpa*	(Irmisch et al., 2013a)
		CYP79D6v4	Herbivore induced •	*Populus nigra*	(Irmisch et al., 2013b; McCormick et al., 2014)
		CYP79D60/ CYP70D61	Jasmonic acid induced •	*Erythroxylum fischeri*	(Luck et al., 2016)
		CYP79D62	Jasmonic acid induced •	*Erythroxylum coca*	(Luck et al., 2016)
		Unknown	Floral scent •	*Albizzia julibrissin*	(Mottram and Flament, 1996)
		Unknown	In flower extract •	*Gaura drummondii*	(Shaver et al., 1997)
		Unknown	Floral scent •	*Silene* sp.	(Jürgens et al., 2002)
		Unknown	Floral scent •	*Nicotiana* sp.	(Raguso et al., 2003)
		Unknown	Herbivore induced •	*Laburnum anagyroides*	(Van Den Boom et al., 2004)
		Unknown	Herbivore induced •	*Glycine max*	(Van Den Boom et al., 2004)
		Unknown	Herbivore induced •	*Robinia pseudoacacia*	(Van Den Boom et al., 2004)
		Unknown	Herbivore induced •	*L. anagyroides*	(Van Den Boom et al., 2004)
		Unknown	Herbivore induced •	*Solanum melongena*	(Van Den Boom et al., 2004)
		Unknown	Induced by citrus canker •	*Citrus paradisi*	(Zhang and Hartung, 2005)
		Unknown	Herbivore induced •	*Phaseolus vulgaris*	(Wei et al., 2006)
		Unknown	*Unknown*	*Asimina triloba*	(Goodrich et al., 2006)
		Unknown	Floral scent •	*Oenothera* sp. Section Lavauxia	(Raguso et al., 2007)

Table 1. Structurally Different Oximes Identified in Plants.

(Continued on next page)

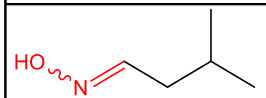
Oxime	Precursor	CYP79	Endpoint	Plant species	Reference
3-methylbutyraldoxime	Leucine	CYP79D6v3/ CYP79D7v2	Herbivore induced •	*P. trichocarpa*	(Irmisch et al., 2013a)
(3-methylbutanal oxime)		CYP79D6v4	Herbivore induced •	*P. nigra*	(Irmisch et al., 2013b; McCormick et al., 2014)
		CYP79A8/ CYP79A12	Hydroxynitrile glucosides •	*Hordeum vulgare*	(Knoch et al., 2016)
		CYP79D60/ CYP70D61	Jasmonic acid induced •	*E. fischeri*	(Luck et al., 2016)
		CYP79D62	Jasmonic acid induced •	*E. coca*	(Luck et al., 2016)
		Unknown	*Unknown*	*Datura sp.*	(Knudsen and Tollsten, 1993)
		Unknown	*Unknown*	*Hedychium coronarium*	(Knudsen and Tollsten, 1993)
		Unknown	*Unknown*	*Silene nutans*	(Knudsen and Tollsten, 1993)
		Unknown	*Unknown*	*Epidendrum ciliare*	(Knudsen and Tollsten, 1993)
		Unknown	Floral scent •	*Anthriscus sylvestris*	(Borg-Karlson et al., 1993)
		Unknown	Floral scent •	*A. julibrissin*	(Mottram and Flament, 1996)
		Unknown	Floral scent •	*Phlox paniculata*	(Andersson et al., 2002)
		Unknown	Floral scent •	*Warszewiczia coccinea*	(Andersson et al., 2002)
		Unknown	Herbivore induced •	*R. pseudo-acacia*	(Van Den Boom et al., 2004)
		Unknown	Herbivore induced •	*L. anagyroides*	(Van Den Boom et al., 2004)
		Unknown	Induced by citrus canker •	*C. paradisi*	(Zhang and Hartung, 2005)
		Unknown	Herbivore induced •	*P. vulgaris*	(Wei et al., 2006)
		Unknown	*Unknown*	*A. triloba*	(Goodrich et al., 2006)
		Unknown	Floral scent •	*Oenothera* sp. Section Lavauxia	(Raguso et al., 2007)

Table 1. ***Continued***

(Continued on next page)

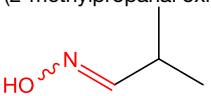
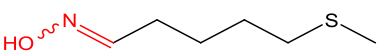
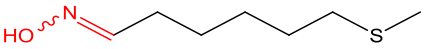
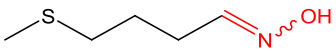
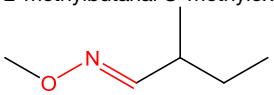
Oxime	Precursor	CYP79	Endpoint	Plant species	Reference
Isobutyraldoxime (2-methylpropanal oxime) 	Valine	CYP79D1/ CYP79D2	Linamarin •	*M. esculenta*	(Andersen et al., 2000)
		CYP79D15	Linamarin •	*T. repens*	(Olsen et al., 2008)
		CYP79D3/ CYP79D4	Linamarin •	*L. japonicus*	(Forslund et al., 2004; Saito et al., 2012)
		Unknown	Linamarin •	*Linum usitatissimum*	(Tapper et al., 1967)
		Unknown	Herbivore induced •	*Gerbera jamesonii*	(Krips et al., 1999)
		Unknown	Floral scent •	*Nicotiana* sp.	(Raguso et al., 2003)
		Unknown	Herbivore induced •	*G. max*	(Van Den Boom et al., 2004)
		Unknown	Herbivore induced •	*R. pseudo-acacia*	(Van Den Boom et al., 2004)
		Unknown	Herbivore induced •	*P. vulgaris*	(Finidori-Logli et al., 1996; Wei et al., 2006)
		Unknown	Floral scent •	*Oenothera* sp. Section Lavauxia	(Raguso et al., 2007)
		Unknown	Herbivore induced •	*P. trichocarpa*	(Irmisch et al., 2013a)
5-methylthiopentanaldoxime  6-methylthiohexanaldoxime 	Chain elongated forms of methionine	CYP79F1/ CYP79F2	Aliphatic glucosinolates •	*Arabidopsis thaliana*	(Hansen et al., 2001; Chen et al., 2003)
4-methylthiobutyraldoxime (4-methylthiobutanal oxime) 	Homomethionine	*Unknown*	Sinigrin •/Alliarinoside •	*Alliaria petiolata*	(Matsuo, 1968; Frisch et al., 2015)
2-methylbutanal *O*-methyloxime 		*Unknown*	Herbivore induced •	*Cucumis sativus*	(Dicke et al., 1990; Takabayashi et al., 1994; Agrawal et al., 2002)
		Unknown	Herbivore induced •	*Zea mays*	(Takabayashi et al., 1995)
		Unknown	Herbivore induced •	*Phaseolus lunatus*	(Dicke et al., 1999; de Boer et al., 2008)
		Unknown	Herbivore induced •	*G. jamesonii*	(Krips et al., 1999)
		Unknown	Herbivore induced •	*R. pseudo-acacia*	(Van Den Boom et al., 2004)
		Unknown	Constitutively/herbivore induced •	*S. melongena*	(Van Den Boom et al., 2004)

Table 1. ***Continued***

(Continued on next page)

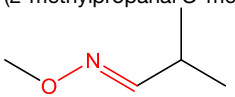
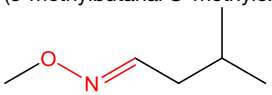
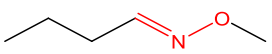
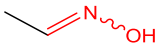
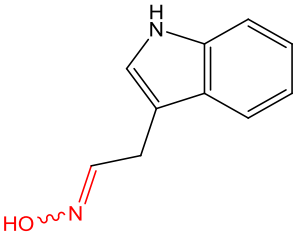
Oxime	Precursor	CYP79	Endpoint	Plant species	Reference
Isobutyraldehyde *O*-methyloxime (2-methylpropanal *O*-methyloxime) 		*Unknown*	Herbivore induced •	*Z. mays*	(Takabayashi et al., 1995)
		Unknown	Herbivore induced •	*P. lunatus*	(Dicke et al., 1999)
		Unknown	Herbivore induced •	*G. jamesonii*	(Krips et al., 1999)
		Unknown	Herbivore induced •	*R. pseudo-acacia*	(Van Den Boom et al., 2004)
		Unknown	Herbivore induced •	*S. melongena*	(Van Den Boom et al., 2004)
Isovaleraldehyde *O*-methyloxime (3-methylbutanal *O*-methyloxime) 		*Unknown*	Herbivore induced •	*Malus domestica*	(Takabayashi et al., 1991)
		Unknown	Herbivore induced •	*C. sativus*	(Dicke et al., 1990; Takabayashi et al., 1994; Agrawal et al., 2002; de Boer et al., 2008)
		Unknown	Herbivore induced •	*R. pseudo-acacia*	(Van Den Boom et al., 2004)
		Unknown	Herbivore induced •	*S. melongena*	(Van Den Boom et al., 2004)
Butyraldehyde *O*-methyloxime (butanal *O*-methyloxime) 		*Unknown*	Herbivore induced •	*Z. mays*	(Takabayashi et al., 1995)
Acetaldoxime (ethanal oxime) 		*Unknown*	Formed during *in vivo* nitrate reduction •	*G. max*	(Mulvaney and Hageman, 1984)
Aromatic					
Indole-3-acetaldoxime (3-indolylethanal oxime) 	Tryptophan	CYP79B2/ CYP79B3	Indole-3-acetic acid •/ indole gluosinolate •/ camalexin •	*A. thaliana*	(Hull et al., 2000; Mikkelsen et al., 2002; Glawischnig et al., 2004)
		CYP79B1	Indole-3-acetic acid •/ indole gluosinolate •	*Sinapis alba*	(Naur et al., 2003a)
		CYP79D6v3/ CYP79D7v2	Herbivore induced •	*P. trichocarpa*	(Irmisch et al., 2013a)
		CYP79D6v4	Herbivore induced •	*P. nigra*	(Irmisch et al., 2013b; McCormick et al., 2014)
		CYP79A61	Indole-3-acetic acid •	*Z. mays*	(Irmisch et al., 2015)
		CYP79D60/ CYP79D61	Jasmonic acid induced •	*E. fischeri*	(Luck et al., 2016)
		CYP79D62/ CYP79D63	Jasmonic acid induced •	*E. coca*	(Luck et al., 2016)
		Unknown	Enzymatic conversion	Cruciferae members	(Kindl, 1968)

Table 1. ***Continued***

(Continued on next page)

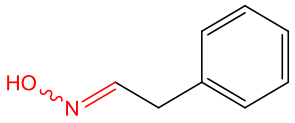
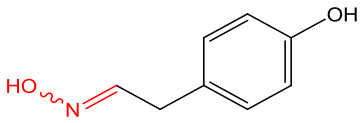
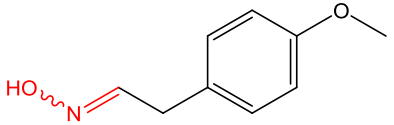
Oxime	Precursor	CYP79	Endpoint	Plant species	Reference
Phenylacetaldoxime (phenylethanal oxime) 	L-phenylalanine	CYP79A2	Benzylglucosinolate •	*A. thaliana*	(Wittstock and Halkier, 2000)
		CYP79D6v3/ CYP79D7v2	Herbivore induced •	*P. trichocarpa*	(Irmisch et al., 2013a)
		CYP79D6v4	Herbivore induced •	*P. nigra*	(Irmisch et al., 2013b; McCormick et al., 2014)
		CYP79D16	Prunasin/amygdalin •	*Prunus mume*	(Yamaguchi et al., 2014)
		CYP79A61	Benzyl cyanide •	*Z. mays*	(Irmisch et al., 2015)
		CYP79D60/ CYP70D61	Jasmonic acid induced •	*E. fischeri*	(Luck et al., 2016)
		CYP79D62	Jasmonic acid induced •	*E. coca*	(Luck et al., 2016)
		Unknown	Glucotropaeolin •	*Tropaeolum majus*	(Underhill, 1967)
		Unknown	Extracted from flowers •	*Citrus unshiu*	(Sakurai et al., 1979)
		Unknown	Benzylglucosinolate •/ prunasin •	*Carica papaya*, *C. quercifolia* (syn. *C. hastate*)	(Olafsdottir et al., 2002)
		Unknown	Floral scent •	*Oenothera* sp. Section Lavauxia	(Raguso et al., 2007)
		Unknown	Floral scent •	*Calanthe sylvatica*	(Delle-Vedove et al., 2011)
p-hydroxyphenylacetaldoxime (4-hydroxyphenylethanal oxime) 	L-tyrosine	CYP79A1	Dhurrin •	*Sorghum bicolor*	(Koch et al., 1995; Sibbesen et al., 1995)
		CYP79E1/ CYP79E2	Triglochinin •	*Triglochin maritima*	(Nielsen and Møller, 1999)
		CYP79D6v3	Herbivore induced •	*P. trichocarpa*	(Irmisch et al., 2013a)
		CYP79D6v4	Herbivore induced •	*P. nigra*	(Irmisch et al., 2013b; McCormick et al., 2014)
		CYP79D60/ CYP70D61	Jasmonic acid induced •	*E. fischeri*	(Luck et al., 2016)
		CYP79D62	Jasmonic acid induced •	*E. coca*	(Luck et al., 2016)
		CYP79A188	Taxiphyllin •	*Taxus baccata*	(Luck et al., 2017)
		Unknown	Tyrosol •	*S. alba*	(Kindl and Schiefer, 1971)
p-methoxyphenylacetaldoxime (4-methoxyphenylethanal oxime) 		*Unknown*	*p*-methoxyphenylmethyl alcohol •	*Aubrietia deltoidea*, *A. hybrida*	(Kindl and Schiefer, 1971)

Table 1. ***Continued***

(Continued on next page)

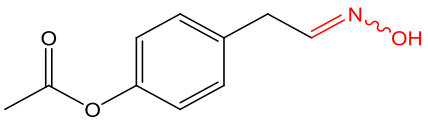
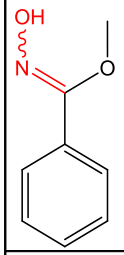
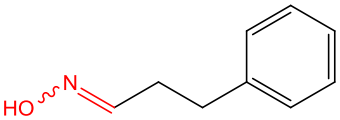
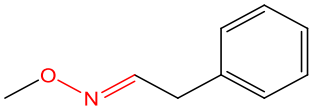
Oxime	Precursor	CYP79	Endpoint	Plant species	Reference
p-acetoxyphenylacetaldoxime (4-*O*-acetylphenylethanal oxime) 		*Unknown*	Glucosinalbin •	*Unknown*	(Benn, 1965)
Methoxyphenyl oxime (methyl *N*-hydroxybenzimidate) 		*Unknown*	Herbivore induced •	*Malus* sp.	(Wang et al., 2014)
3-phenylpropionaldoxime (3-phenylpropanal oxime) 	L-phenylalanine chain elongated into 2-amino-4-phenylbutyric acid	*Unknown*	Gluconasturtiin •	*Nasturtium officinale*	(Underhill, 1967)
Phenylacetaldehyde *O*-methyl oxime (4-(3-methylbut-2-en-1-yl)phenyl-2-oxoethanal oxime) 		*Unknown*	Herbivore induced •	*S. melongena*	(Van Den Boom et al., 2004)
		Unknown	Herbivore induced •	*R. pseudo-acacia*	(Van Den Boom et al., 2004)
		Unknown	Induced by citrus canker •	*C. paradisi*	(Zhang and Hartung, 2005)

Table 1. ***Continued***

(Continued on next page)

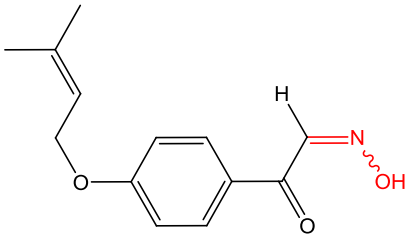
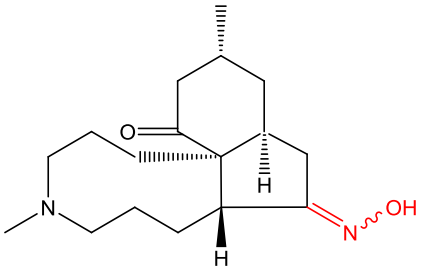
Oxime	Precursor	CYP79	Endpoint	Plant species	Reference
Other					
Citaldoxime 		*Unknown*	Extracted from roots •	*Citrus sinensis*	(Ito et al., 1990)
Lycoposerramine-B 		*Unknown*	Isolated from plant material •	*Lycopodium serratum*	(Katakawa et al., 2005)
Canaline glyoxylate oxime 		*Unknown*	Breakdown product of the plant non-protein amino acid L-canavanine •	*Canavalia ensiformis*	(Cooper, 1984; Rosenthal and Berge, 1989)

Table 1. *Continued*

A list of structurally diverse oximes identified in plants, their structure and precursor, identified CYP79 enzyme, endpoint, plant species, and reference. For future studies, updated information on the presence of oximes and oxime ethers in plants may be obtained from SciFinder. Searches carried out September 15 2017 on "Oximes in plants" and "Oxime ethers in plants" gave 437 and 192 references, respectively.

The oxime function is marked in red in all structures. Color dots indicate type of metabolite/endpoint and correspond to colors in Figure 4.

• Cyanogenic glucoside/hydroxynitrile glucoside, • glucosinolate, • volatile emission, • auxin, • others.

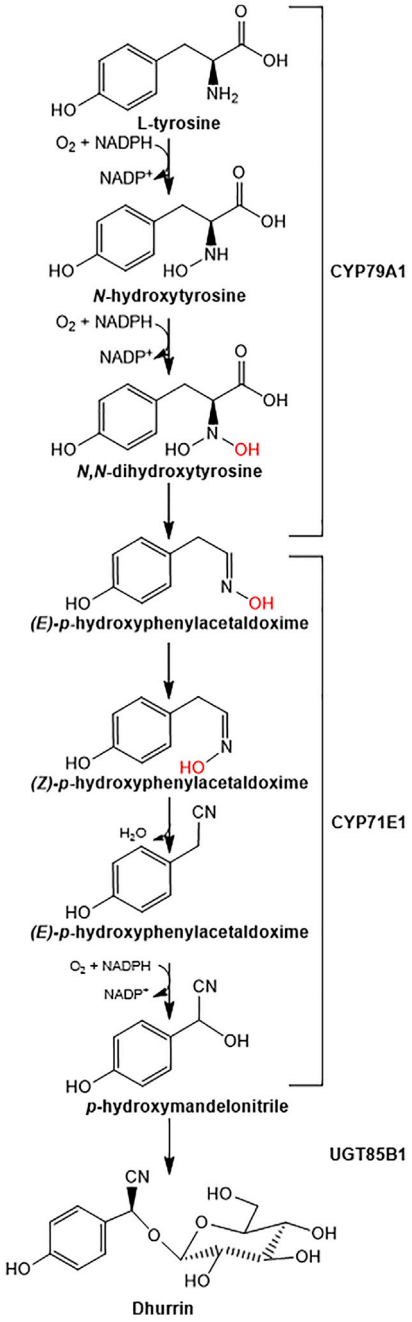


Figure 3. Biosynthetic Pathway of the Cyanogenic Glucoside Dhurrin.

CYP79A1 from sorghum (*Sorghum bicolor*) catalyzes the conversion of the amino acid L-tyrosine to the corresponding oxime, (*E*)-*p*-hydroxyphenylacetaldoxime in cyanogenic glucoside biosynthesis. CYP71E1 catalyzes the subsequent rearrangement of the E-oxime into a Z-oxime, the unusual dehydration reaction, and the subsequent decarboxylation yielding the *p*-hydroxymandelonitrile. Cytochrome P450 oxidoreductase provides the electrons to drive the catalytic cycle. Finally, a glucosyltransferase from the UGT85 family catalyzes glucosylation of the labile cyanohydrin to form dhurrin.

the principal non-protein amino acid L-canavanine from jack bean (*Canavalia ensiformis*), and the alkaloid oxime lycoposerramine-B was isolated from club moss (*Lycopodium serratum*) (Katakawa et al., 2005). Based on the current knowledge, we speculate that many more oximes exist in plant species, and that their detection will be greatly facilitated by the technological advances in analytical chemistry. Despite the overall degree of oxime diversity, little is known about the function of these metabolites.

DO ALL HIGHER PLANTS PRODUCE OXIMES?

The direct biosynthetic route to the amino acid-derived oximes in seed plants is catalyzed by a cytochrome P450 monooxygenase (P450) from the CYP79 family (CYP79). P450s are one of the largest plant enzyme families supporting both general and specialized metabolism, with the encoding genes representing 1% of all plant protein coding genes (Nelson and Werck-Reichhart, 2011). P450 enzymes from the CYP79 family belong to the CYP71 clan, a clan assigned to functions in plant specialized metabolism and comprising more than 50% of all plants (Nelson and Werck-Reichhart, 2011). To date, all functionally characterized CYP79s have been found to catalyze the same standard reaction: the conversion of amino acids into oximes. The first characterized CYP79 enzyme, CYP79A1 from sorghum (*Sorghum bicolor*), was shown to convert L-tyrosine to (*E*)-*p*-hydroxyphenylacetaldoxime in the biosynthesis of the cyanogenic glucoside dhurrin (Koch et al., 1995; Sibbesen et al., 1995; Clausen et al., 2015). Mechanistically, CYP79A1 catalyzes the conversion via two N-hydroxylation steps to afford a highly unstable *N,N*-dihydroxytyrosine, which is dehydrated to form an α-nitrosocarboxylic acid with 100% retention of the oxygen atom introduced at the second N-hydroxylation reaction. Finally, decarboxylation via a cyclic transition state leads to the formation of (*E*)-*p*-hydroxyphenylacetaldoxime (Figure 3). The 100% retention of the oxygen atom introduced in the second N-hydroxylation step demonstrates that all intermediates in the CYP79A1-catalyzed conversion are tightly bound within the catalytic site of CYP79A1, permitting no rotation around the C–N single bond present in the intermediates (Halkier et al., 1991; Vazquez-Albacete et al., 2017). Due to the fact that all CYP79s characterized to date catalyze the conversion of amino acids to oximes, and the presence of conserved family-specific motifs (Gotoh, 1992; Gotoh et al., 2014), it is hypothesized that mechanistically, all CYP79s catalyze the production of E-oximes via this pathway involving *N,N*-dihydroxylation of the parent amino acid (Møller and Conn, 1979).

CYP79s were later demonstrated to catalyze the initial step in biosynthesis of cyanogenic glucosides derived from aliphatic as well as aromatic parent amino acids in other plant species (Table 1) (Andersen et al., 2000; Forslund et al., 2004; Olsen et al., 2008; Yamaguchi et al., 2014; Knoch et al., 2016; Luck et al., 2017). Based on the presence of conserved sequence motifs and high overall sequence homology to the sorghum CYP79A1 sequence, CYP79s were also demonstrated to be involved in glucosinolate biosynthesis (Halkier and Gershenzon, 2006). An account of different oximes detected in different plant species and formed from amino acids by the activity of CYP79 enzymes is provided in Table 1.

As more sequencing data have become available, it is apparent that CYP79s are widespread in higher plants. Regarding lower

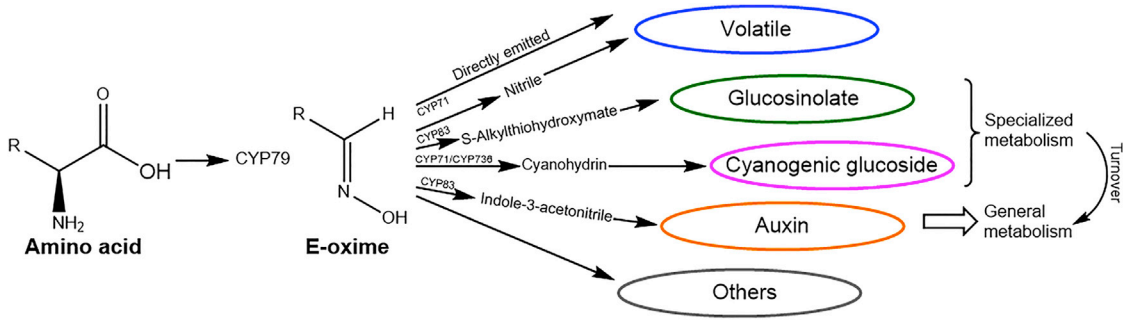


Figure 4. An Overview of Oxime-Derived Plant Metabolites.
Overview of the various types of metabolites formed from amino acids via oximes in CYP79-catalyzed reactions, showing relevant oxime-metabolizing enzymes and intermediates toward the endpoint. Colors encircling each type of endpoint correspond to colors in Table 1.

plants, CYP79s have so far appeared absent in ferns and bryophytes (Nelson and Werck-Reichhart, 2011; Luck et al., 2017). This is noteworthy, as some fern species produce cyanogenic glycosides (Harper et al., 1976) that theoretically would be formed with an oxime as a key intermediate in the pathway. CYP79s arose in gymnosperms, and analyses of conifers has shown the presence of CYP79s in some families and absence in others such as the Pinaceae (Luck et al., 2017). In flowering plants, genes encoding enzymes from the CYP79 family are present in all sequenced or otherwise analyzed eudicots and non-eudicot angiosperms (Nelson and Werck-Reichhart, 2011). All flowering plants thus have the CYP79 blueprint to, theoretically, produce oximes.

FUNCTIONS OF OXIMES AND OXIME-DERIVED PRODUCTS IN PLANTS

CYP79-catalyzed oxime formation makes the biosynthetic basis for a plethora of plant general and specialized metabolites. The oxime-producing CYP79s are observed to operate together with other P450s from the CYP71 clan, specifically from the CYP71, CYP736, and CYP83 families. P450s from these families are oxime-metabolizing enzymes following the CYP79s in the biosynthetic routes. Oximes are involved in many different functions in plant metabolism, either as an end product or as an intermediate in the production of general and specialized metabolites (Figure 4). In particular, oximes are intermediates in the biosynthesis of the well-known defense compounds cyanogenic glucosides and glucosinolates (Tapper et al., 1967; Underhill, 1967) and in formation of the hormone auxin. Oximes also play a role in direct defense, e.g., phenylacetaldoxime has been identified as an accumulated metabolite functioning as a deterring agent in western balsam poplar (*Populus trichocarpa*) (Irmisch et al., 2013a). In addition, volatile oximes are emitted from a number of different plant species (Table 1) playing a role in plant communication. For many of the identified oxime structures, however, their function remains unknown.

CYANOGENIC GLUCOSIDES

Cyanogenic glucosides (hydroxynitrile glucosides) are α-hydroxnitrile glucosides structurally related to the β- and γ-hydroxynitrile glucosides; however, the latter two do not release toxic hydrogen cyanide upon degradation (Bjarnholt and Møller, 2008). Studies on cyanogenic glucoside (α-hydroxnitrile glucoside) biosynthesis were initiated in 1967 with linen flax (*L. usitatissimum*) seedlings producing linamarin from the amino acid precursor valine (Tapper et al., 1967) and in leaves of cherry laurel (*Prunus laurocerasus*) producing prunasin from phenylalanine (Hahlbrock et al., 1968). The breakthrough in elucidating the entire cyanogenic glucoside pathway came from studies in Eric E. Conn's laboratory using a microsomal system isolated from etiolated seedlings of sorghum to study the biosynthesis of tyrosine-derived dhurrin (MacFarlane et al., 1975; Møller and Conn, 1979, 1980). Today, cyanogenic glucosides in plants are known to be formed from the five protein amino acids tyrosine, phenylalanine, valine, isoleucine, and leucine and from the non-protein amino acid cyclopentenylglycine (Olafsdottir et al., 1992). All except the last have been demonstrated to be converted into the corresponding oximes by the action of CYP79s (Gleadow and Møller, 2014). In the biosynthesis of cyanogenic glucosides and other hydroxynitrile glucosides the E-oximes are converted into cyanohydrins (Figure 4) (Jørgensen et al., 2011; Takos et al., 2011; Clausen et al., 2015; Knoch et al., 2016). This function can be exemplified by CYP71E1 involved in dhurrin biosynthesis in sorghum. CYP71E1 catalyzes the conversion of (*E*)-*p*-hydroxyphenylacetaldoxime into *p*-hydroxymandelonitrile, i.e., an initial unusual structural rearrangement reaction converting the E-oxime into a Z-oxime prior to a dehydration reaction to form a nitrile followed by a classical C-hydroxylation reaction (Figure 3). This also applies for other CYP71 family enzymes catalyzing the second part of cyanogenic glucoside biosynthesis (Jørgensen et al., 2011).

Cyanogenic glucosides are the most common and well-distributed cyanogens in plants, representing a mechanism for defense by the action of specific β-glucosidases resulting in the release of hydrogen cyanide (Gleadow and Woodrow, 2002). Similarly, β- and γ-hydroxynitrile glucosides are defense compounds with oximes as key intermediates in their biosynthesis (Table 1). This is exemplified by barley (*Hordeum vulgare*), which produces the α- (cyanogenic), β-, and γ-hydroxynitrile glucosides: epiheterodendrin, sutherlandin, epidermin, osmaronin, and dihydro-osmaronin (Nielsen et al., 2002). The hydroxynitrile glucosides in barley are all derived from leucine with the barley enzymes CYP79A8 and CYP79A12 producing the oxime intermediate (Table 1). Following, CYP71C113, CYP71L1, and CYP71U5 all catalyze subsequent

dehydration of the oxime to produce the hydroxynitrile. Even though the β- and γ-hydroxynitrile glucosides do not release hydrogen cyanide upon hydrolysis, they have strong effects against fungal infection (Knoch et al., 2016).

The major qualitative and quantitative changes in the accumulation and disappearance of cyanogenic glucosides at different stages of plant ontogeny would imply that cyanogenic glucosides are subject to endogenous turnover. This has previously been demonstrated in sorghum (Adewusi, 1990; Busk and Møller, 2002). Indeed, an endogenous turnover pathway enabling plants to catabolize cyanogenic glucosides without release of toxic hydrogen cyanide has been demonstrated to operate in several cyanogenic plants (Picmanova et al., 2015). The operation of such a pathway identifies cyanogenic glucosides as storage compounds of reduced carbon and nitrogen that on demand can be made available to counteract imbalances in plant general metabolism. The operation of the endogenous turnover pathway has been studied in sorghum, cassava (*Manihot esculenta*), and almond (*Prunus dulcis*). In all three species it involves formation of the corresponding amides, carboxylic acids, and anitriles (defined as products obtained by the loss of the nitrile-group). The turnover of these molecules results in the release of ammonia and glucose (Picmanova et al., 2015; Nielsen et al., 2016). Recently, a role of prunasin and its turnover products in controlling flowering time in *Prunus* species has been proposed (Del Cueto et al., 2017; Ionescu et al., 2017).

The levels of cyanogenic glucosides in the leaves also show a diurnal pattern. The levels were found to be highest at dawn, decreasing rapidly upon exposure to sunlight, and were re-established after sunset and during the night period (Adewusi, 1990; Kongsawadworakul et al., 2009; Fang et al., 2016). This may reflect rapid endogenous turnover during the day to balance carbon fixation by photosynthesis with a pool of reduced nitrogen (Kongsawadworakul et al., 2009). Alternatively, the decrease in cyanogenic glucoside levels in sunlight reflects that the cyanogenic glucosides may function as scavengers of reactive oxygen species (ROS) in a process in which they are converted into amides (Hajek et al., 1974; Sendker and Nahrstedt, 2009).

GLUCOSINOLATES

The first report of oximes as intermediates in the biosynthesis of glucosinolates was based on studies in nasturtium (*T. majus*) where phenylalanine-derived phenylacetaldoxime was found to be a precursor of the glucosinolate glucotropaeolin (Table 1) (Underhill, 1967). Later the full elucidation of the glucosinolate pathway was accomplished using arabidopsis (*Arabidopsis thaliana)* as the experimental system (Halkier and Gershenzon, 2006). At present, glucosinolates are known to be formed from the parent amino acids alanine, valine, leucine, isoleucine, methionine, tyrosine, phenylalanine, and tryptophan as well as from chain-elongated forms of phenylalanine and methionine (Halkier, 2016). In all cases, the first step in glucosinolate biosynthesis is CYP79-catalyzed formation of an oxime intermediate. However, in glucosinolate biosynthesis the oxime-metabolizing CYP83 enzyme is not able to catalyze isomerization from E- to Z-oxime but converts E-oxime directly to the subsequent product. Hence all glucosinolates have preserved the structural organization from the E-oxime (Clausen et al., 2015). The product following the E-oxime is an S-alkylthiohydroximate in glucosinolate biosynthesis (Figure 4) (Naur et al., 2003b; Zhu et al., 2012).

In addition, an indole-3-acetaldoxime-mediated link between indole glucosinolate biosynthesis and phenylpropanoid synthesis has been reported, based on studies of an arabidopsis mutant defective in the gene encoding the oxime-metabolizing enzyme CYP83A1/B1 (Hemm et al., 2003; Kim et al., 2015). Specifically, glucosinolates are key defense compounds in the Brassicales, hydrolyzed by specific thioglycosidases (myrosinases) upon tissue disruption in a process releasing numerous toxic constituents including isothiocyanate (Halkier and Gershenzon, 2006; Wittstock et al., 2016).

Glucosinolates may serve as storage compounds of reduced carbon, nitrogen, and sulfur but this process is not fully understood because endogenous turnover pathways remain to be revealed. However, research conducted in relation to plant nutrition suggests that glucosinolates serve especially as sulfur storage compounds (Wittstock et al., 2016). Further, glucosinolate content is diurnally regulated, as well as being regulated through the growth season. The diurnal regulation of the glucosinolate biosynthesis is co-regulated with sulfate assimilation and influenced by light and temperature (Rosa et al., 1996; Pereira et al., 2002; Huseby et al., 2013).

AUXIN AND CAMALEXIN

The biosynthesis of indole glucosinolates is closely linked to the biosynthesis of the auxin indole-3-acetic acid (IAA), with indole-3-acetaldoxime (Table 1) representing a significant point of metabolic bifurcation between general and specialized metabolism. CYP79B2/B3-catalyzed conversion of tryptophan into indole-3-acetaldoxime offers an intermediate for the formation of IAA, indole glucosinolates, and the phytoalexin camalexin in arabidopsis and other Brassicaceae members (Figure 5) (Bak and Feyereisen, 2001; Bak et al., 2001; Glawischnig et al., 2004; Sugawara et al., 2009; Nonhebel et al., 2011; Kong et al., 2015). Auxins were discovered in the 1930s to be regulators of plant growth and development. The biosynthesis of IAA from tryptophan may also proceed by routes not involving indole-3-acetaldoxime as intermediate (Mano and Nemoto, 2012; Kong et al., 2015).

CYP79A61 from maize (*Zea mays*) (Table 1) producing phenylacetaldoxime and indole-3-acetaldoxime is another example of a CYP79 enzyme that is involved in both general and specialized metabolism (Irmisch et al., 2015). A multiplicity of such dual-use functionalities are likely to be discovered when studying CYP79s in the future. Thus, it is speculated that this particular function to catalyze auxin formation is a reason for CYP79s being so widespread across the plant kingdom.

Indole-3-acetaldoxime is also the precursor of plant constituents thought to be important for induced pathogen defense. Examples are the formation of the indole alkaloid camalexin by the action of CYP71A13 (Glawischnig et al., 2004; Nafisi et al., 2007; Klein et al., 2013) and formation of 4-hydroxyindole-3-carbonyl nitrile

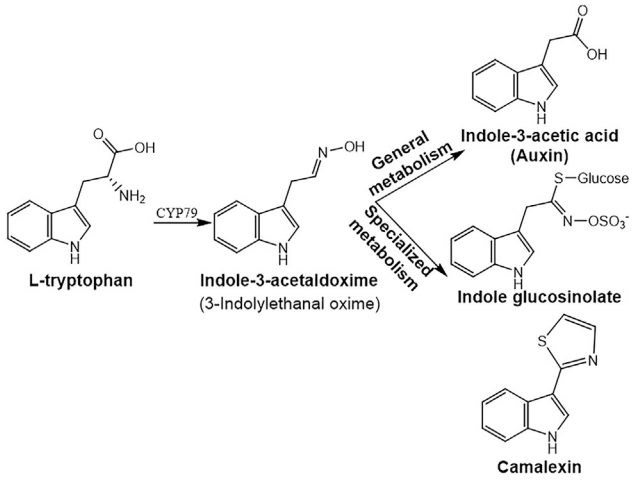


Figure 5. Oxime Represents the Bifurcation Point between General and Specialized Plant Metabolism.
The bifurcation point between general and specialized plant metabolism represented by the oxime, indole-3-acetaldoxime, in the biosynthetic pathways of the phytohormone auxin indole-3-acetic acid, indole glucosinolate, and camalexin (Glawischnig et al., 2004; Nonhebel et al., 2011).

by the action of two P450s, CYP71A12 and CYP82C2 (Rajniak et al., 2015). These compounds strengthen immunity especially to bacterial infections (Rajniak et al., 2015).

PLANTS USE OXIMES IN COMMUNICATION

Oximes are present in the blend of volatile organic compounds (VOCs) produced and released by many plant species (see Table 1) as part of their interaction with the surrounding environment (Knudsen and Tollsten, 1993; Knudsen et al., 2006). The release of VOCs can serve different purposes, e.g., to attract pollinators, deter herbivores, or attract natural enemies of herbivores (Kaiser, 2004; Raguso, 2008; Unsicker et al., 2009). The first oxime detected from flowers was phenylacetaldoxime found in the flower extract from satsuma mandarin (*Citrus unshiu*) (Sakurai et al., 1979). Today oximes are assumed very important in the volatile blend emitted from flowers and leaves as they work as scent modifiers and have a very characteristic musky smell that attracts moths, e.g., as in evening primrose (*Oenothera sp.*) (Goodrich et al., 2006; Raguso et al., 2007). Another example from the same plant family is 2-methylbutyraldoxime found to be the major component in flower extracts of the night blooming *Gaura drummondii* when harvested at night time (Shaver et al., 1997).

In Darwin's orchid (*Angraecum sesquipedale*), a unique blend of aliphatic and aromatic oximes is released during dusk to attract a specialist moth to facilitate pollination (Nielsen and Møller, 2015). Release of a different volatile emission profile from the dorsal sepal, lateral petal, and labellum of the orchid flower serves to direct the moth by contributing to the olfactory image of the flower (Kaiser, 1994; Nielsen and Møller, 2015).

The emitted VOCs may be constitutively produced or induced, e.g., upon herbivory. Convincing evidence documents that oximes play a key role in herbivore-induced volatile response. Thus, two aliphatic oximes were found to be released from bean (*Phaseolus vulgaris*) plants in response to agromyzid flies (Wei et al., 2006). 2- and 3-methylbutyraldoxime emitted from black poplar (*Populus nigra*) were also emitted as a response to gypsy moth (*Lymantria dispar*) caterpillars (McCormick et al., 2014). In all cases, the oxime release reduced the herbivore damage level. Plant protection involving a third trophic level has also been demonstrated based on emission of herbivore-induced volatile blends containing oximes that function as essential cues attracting herbivore parasitoids (Finidori-Logli et al., 1996; McCormick et al., 2014). The herbivore-induced production of VOCs can be mimicked by jasmonic acid treatment inducing production of aldoximes and other N-containing volatiles as discovered in lima beans (*Phaseolus lunatus*) and *Erythroxylum* species (Dicke et al., 1999; Luck et al., 2016) (Table 1).

CYP71s able to catalyze conversion of an E- to the corresponding Z-geometrical oxime and a following dehydration reaction of the Z-oxime into the nitrile but without catalyzing the subsequent C-hydroxylation of the nitrile have also been identified (Irmisch et al., 2014; Yamaguchi et al., 2016). Thus, the formed nitriles can be either end products (Irmisch et al., 2014; Yamaguchi et al., 2016) or further converted into nitro compounds, alcohols, aldehydes, or esters (Irmisch et al., 2014; Nielsen and Møller, 2015).

A number of CYP79s involved in production of volatile oximes have been identified (Table 1), and upregulation of the genes encoding the responsible CYP79s has been demonstrated to be herbivore induced (Irmisch et al., 2013a, 2013b, 2015). In maize (*Z. mays*), herbivory leads to an upregulation of the CYP79A61-encoding transcript resulting in increased accumulation of phenylacetaldoxime and indol-3-acetaldoxime accompanied by increased levels of IAA (Irmisch et al., 2015). In some cases, the oximes produced are further converted into the corresponding nitriles by the action of an additional P450 belonging to the CYP71 clan (Irmisch et al., 2014). In Darwin's orchid, a proportion of the phenylacetaldoxime formed is converted into other VOCs such as phenylacetaldehyde, 2-phenylethanol, 2-phenylethanol acetate, and 2-phenylethanol valerate (Nielsen and Møller, 2015).

In several plant species, methylated oximes have been found to be specifically released upon herbivore attack (Table 1) (Takabayashi et al., 1994, 1995; Simpraga et al., 2016). The general occurrence of methylated oximes in plants has not been studied thoroughly and is definitely an area that needs further investigation, especially with respect to their involvement in the option of uninfested plants to benefit from the ability of infested neighbor plants to attract herbivore predators (Takabayashi et al., 1991; Simpraga et al., 2016).

POTENTIAL FUNCTIONS OF MORE COMPLEX OXIME OR OXIME-DERIVED STRUCTURES

In addition to the already mentioned compounds, CYP79-derived oximes may function as intermediates in the biosynthesis of other

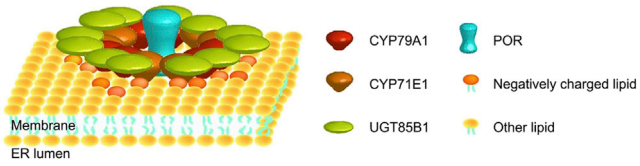


Figure 6. Metabolon Formation Encompassing Enzymes Involved in Dhurrin Biosynthesis.
A model of the dhurrin biosynthesis channeled via metabolon formation encompassing CYP79A1, CYP71E1, UGT85B1, and P450 oxidoreductase (POR). The metabolon involves higher-order clusters and enrichment of negatively charged phospholipids (from Laursen et al., 2016).

specialized metabolites. An example is tyrosol, a C_6–C_2 phenolic anti-oxidant, derived from tyrosine via *p*-hydroxyphenylacetaldoxime (Kindl and Schiefer, 1971). Tyrosol is present in olive oil and green tea and is, like its glucoside salidroside, appreciated for its health-promoting properties (Xue et al., 2017). Tyrosol is also a bitter constituent of hops (Oladokun et al., 2017). Tyrosol biosynthesis, however, needs reinvestigation since biosynthetic pathways operating via tyramine or *p*-hydroxyphenylpyruvic acid have also been reported (Xue et al., 2017).

In addition to the amino acid-derived oxime derivatives, three oximes of more complex structures have been elucidated from plants (see Table 1). The non-protein amino acid canaline is present in canavanine-producing legumes such as jack bean (*C. ensiformis*) and formed from canavanine by the action of arginase. In jack bean, the catabolism of canaline proceeds via formation of canaline glyoxylate oxime (Cooper, 1984; Rosenthal and Berge, 1989). Canaline is the only known naturally occurring non-protein amino acid, being an O-alkyl hydroxylamine, and it has been demonstrated to be a strong insecticide (Rosenthal, 1997). In a non-enzyme-catalyzed process, canaline readily reacts with keto acids and aldehydes to form oximes. Part of its toxicity may be related to its reaction with pyridoxal phosphate, a co-factor of vitamin B_6-dependent enzymes. In sweet oranges (*C. sinensis*) citraldoxime was identified and found to be identical to an anti-fungal stress metabolite known from citrus fruits (Ito et al., 1990). The alkaloid lycoposerramine-B contains an oxime function and has been isolated from club moss (*L. serratum*). The function of lycoposerramine-B is unknown (Katakawa et al., 2005).

CAN THE FUNCTIONS OF OXIMES IN PLANTS BE PREDICTED BY THEIR METABOLIZING ENZYMES?

In all plant species hitherto examined for the genomic localization of the genes encoding the biosynthetic pathway of hydroxynitrile glucosides, the genes have been found to be organized in gene clusters in the genome (Takos et al., 2011). This also applies for the *CYP71* genes producing β- and γ-hydroxynitrile glucosides in barley (Knoch et al., 2016). In sorghum and barley, transporters of the hydroxynitrile glucosides are likewise embedded in the gene clusters (Darbani et al., 2016).

The future availability of genome sequences of a rapidly increasing number of plant species and the possible positioning of the genes encoding oxime biosynthesis as well as formation of oxime-derived bioactive constituents and their transporters within gene clusters are expected to guide identification of missing genes encoding such conversions and to facilitate determination of the function of the products formed. In this context, the presence of genes encoding P450s belonging to the CYP71 clan should be given specific attention because the CYPs present in this clan are not functionally conserved.

POSSIBLE PRESENCE OF TRANSOXIMASES IN PLANTS

A few reports in the literature point to the existence of transoximases in plants. Dependent on the occurrence and substrate specificities of such transoximases, the oxime-functional group of oximes known to be produced in plants, e.g., from the action of CYP79 family enzymes, could in theory be transferred to any aldehyde or keto compound present. Such compounds may have biological functions. In plants, transoximases specific for three individual donor oximes (glucosoxime, α-ketoglutaric acid oxime, acetoxime) have been identified in spinach, mulberry, and wheat (Omura and Tsutsumi, 1968). Transoximation reactions have also been demonstrated in animals such as silkworm, fowl, and rabbit (Omura and Tsutsumi, 1968). No recent studies on transoximases and their activity are available, opening up for revisiting this entire research area using modern technologies.

THE METABOLIC HIGHWAY

Oximes are highly reactive molecules not necessarily subject to storage since most oximes formed in plants are emitted as volatiles. When oximes are released as products in biosynthetic reactions, they are typically converted into the corresponding alcohols, aldehydes, or carboxylic acids. Residual amounts of aldoximes are converted to glucosides, which presumably are stored in the plant vacuole (Bak et al., 2000; Blomstedt et al., 2012; Clausen et al., 2015). When serving as a precursor balancing the production of the plant hormone IAA, indole-3-acetaldoxime may also be stored as a glucoside. When oximes are produced *in planta* as intermediates, e.g., in the biosynthesis of cyanogenic glucosides, avoidance of self-toxicity is orchestrated by encapsulation of the oxime by metabolic channeling and metabolon formation. Metabolons are dynamic non-stoichiometric enzyme complexes formed by non-covalent protein–protein interactions possibly with one or more membrane-bound components functioning as nucleation sites (Møller and Conn, 1980; Møller, 2010; Laursen et al., 2016; Bassard et al., 2017). As an example, the dhurrin biosynthetic pathway in sorghum has been demonstrated to be efficiently channeled via metabolon formation encompassing two membrane-bound P450s (CYP79A1, CYP71E1), a UDP-glucosyl transferase (UGT85B1), and P450 oxidoreductase (Figure 6) (Møller and Conn, 1980; Laursen et al., 2016). Metabolon assembly and disassembly may be controlled by environmental challenges like fungal attack resulting in release of ROS that at the site of infection may reach levels resulting in denaturation of the labile CYP71E1 enzyme (Møller, 2010). This would permit ''on demand'' formation of bioactive oximes to combat the fungal infection.

DIFFERENT FUNCTIONALITIES OF E- AND Z-OXIMES

Oximes may exist as two geometrical isomeric forms assigned either an E or a Z configuration (Figure 1A). The chemical and biological properties of these two geometrical forms differ. Sorghum produces the tyrosine-derived cyanogenic glucoside dhurrin that has served as the experimental model system for studies of cyanogenic glucosides biosynthesis (Møller and Conn, 1979, 1980; Halkier and Møller, 1990). The biosynthetic pathway of dhurrin was shown to involve the sequential production of (*E*)- and (*Z*)-*p*-hydroxyphenylacetaldoxime as intermediates (Halkier et al., 1989). In a study using microsomes from wild-type sorghum and from the *tcd1* mutant with an inactive CYP79A1 (Halkier and Møller, 1990; Blomstedt et al., 2012; Clausen et al., 2015) it was demonstrated that CYP79A1 catalyzes the conversion of tyrosine into (*E*)-*p*-hydroxyphenylacetaldoxime and that CYP71E1 catalyzes subsequent rearrangement of the E-oxime into the Z-oxime and its subsequent dehydration to *p*-hydroxyphenylacetonitrile. The geometrical isomers may also interconvert non-enzymatically to establish chemical equilibrium. At neutral pH, the equilibrium ratio for (*E*)- and (*Z*)-*p*-hydroxyphenylacetaldoxime is 58:42 and is established after several days (Halkier et al., 1989). Glucosinolates retain the configuration of the E-oxime in their core structure. In arabidopsis, it was demonstrated that CYP83B1 does not catalyze the rearrangement of (*E*)-*p*-hydroxyphenylacetaldoxime into the Z form but instead catalyzes its conversion into an S-alkylthiohydroximate. This defines the E-oxime as the branchpoint between cyanogenic glucoside and glucosinolate synthesis (Figure 4) (Clausen et al., 2015).

The functional differences between E- and Z-oximes extend much further than their different roles in cyanogenic glucoside and glucosinolate biosynthesis. In general, oximes inhibit the ability of oxygenic organisms to produce ATP by inhibiting the mitochondrial oxidase of the respiratory chain and thus the generation of ATP (Sakurada et al., 2009; Møller, 2010). In this context, it is interesting that a widely distributed property among bacteria (e.g., actinomyces) and fungi (e.g., some yeasts) is their ability to produce dehydratases able to specifically convert Z-oximes into the corresponding nitriles (Kato et al., 2000a, 2000b; Kato and Asano, 2005; Kato et al., 2007; Pinakoulaki et al., 2011). This applies to *Fusarium graminearum*, the head blight fungus of wheat and barley, which produces an oxime dehydratase showing activity to aromatic and aliphatic oximes such as phenylacetaldoxime, *n*-butyraldoxime, isobutyraldoxime, *n*-valeraldoxime, and isovaleraldoxime (Kato and Asano, 2005). These oximes all display a noticeable high structure similarity to the oxime intermediates involved in the synthesis of cyanogenic glucosides present in wheat (Erb et al., 1981; Pitsch et al., 1984) and barley (Nielsen et al., 2002; Knoch et al., 2016). In addition, *F. graminearum* possesses a nitrilase and an amidase converting the nitriles formed into the corresponding amides and carboxylic acids. Thus the head blight fungus of wheat and barley would appear to possess a mechanism to detoxify Z-oximes possibly released from the cyanogenic glucoside pathways in its host plants upon denaturation of the CYP71 enzyme (Møller, 2010). Remarkably, the head blight fungus is apparently not able to detoxify the corresponding E-oximes. The "Z-aldoxime–nitrile pathway" appears widespread among microorganisms (Kato et al., 2000b; Sawai et al., 2009), some of which also possess the ability to produce the oximes from amino acids by an unknown mechanism (Kato et al., 2007).

The ability of microorganisms to convert aldoximes into nitriles through the action of dehydratases is found throughout different environments. Examples of microorganisms known for their ability to degrade oximes by aldoxime dehydratases are the glutaronitrile degrader *Pseudomonas* sp. K-9 (Kato and Asano, 2006) and *Bacillus* sp. converting (*Z*)-phenylacetaldoxime to phenylacetonitrile (Kato et al., 2000a; Kobayashi et al., 2006). None of the microbial dehydratases characterized were P450s but some contained loosely bound protoheme IX as a prosthetic group (Kato and Asano, 2005). Similar enzyme specificities have been found in animals, but now catalyzed by a P450 enzyme. Thus CYP3A4 from human liver was found to specifically catalyze dehydration of (*Z*)-benzaldoxime (Boucher et al., 1994), and in horse liver, aliphatic E-oximes were found to inhibit alcohol dehydrogenase by forming a ternary complex with the enzyme and NAD^+ (Sigman et al., 1982).

EVOLUTIONARY ORIGIN OF OXIME FORMATION ON PLANET EARTH

The route and time point for the first appearance of oxime compounds on planet Earth and in the interstellar environment are obscure and conjectural. Several constituents have been hypothesized as present as well as absent in the atmosphere of the early Earth and in the Earth primordial soup including submarine hydrothermal systems (Miller and Urey, 1959; Tian et al., 2005; Coveney et al., 2012; Pulliam et al., 2012; McGuire et al., 2015; Rotelli et al., 2016). These include methane, hydrogen, nitrogen, ammonia, hydroxylamine, formaldehyde, hydrogen cyanide, carbon dioxide, and water (Miller, 1953; Miller and Urey, 1959; Charnley et al., 2001; Snow et al., 2007; Saladino et al., 2009, 2012; Coveney et al., 2012). In a pre-biotic world, oximes may have been formed in a simple chemical reaction between formaldehyde and hydroxylamine. Reactions between hydroxylamine and other aldehydes or keto compounds would give rise to formation of a structurally highly diverse number of oximes. The possible origins of oximes in nature as discussed above is hypothetical. It remains a possibility that hydrogen cyanide, hydroxylamine, and oximes have been among the early constituents present on planet Earth, and thus might have been among the early building blocks of life. The availability of these reactive small molecules would favor their incorporation into more complex chemical structures. Thus simple condensation reactions of hydrogen cyanide may give rise to formation of multiple organic compounds including adenine (Roy and Schleyer, 2010).

In biotic environments, hydroxylamine is formed as part of microbial nitrification where ammonium is oxidized to nitrite via hydroxylamine (Liu et al., 2014, 2016). When present in a biotic environment, organisms exposed to oximes would be expected to evolve an ability to use them as nitrogen and carbon sources. Hypothetically, this might initially have involved transoximase-catalyzed conversion of available oximes into

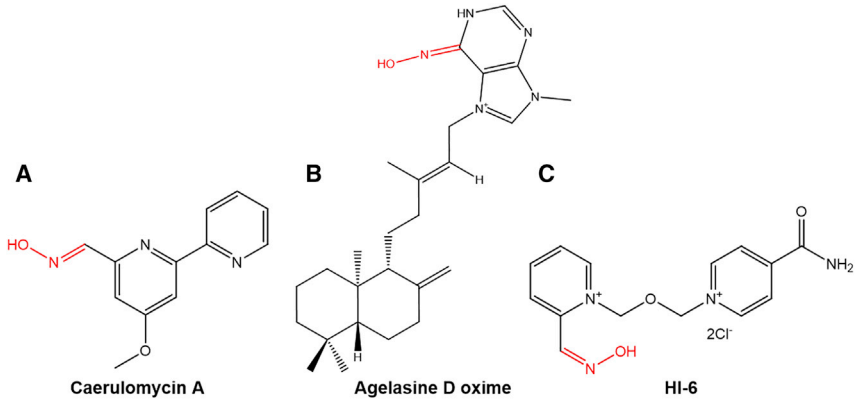


Figure 7. Complex Oxime Structures.
(A) Caerulomycin A isolated from *Streptomyces caeruleus* is an example of an oxime from microbial specialized metabolism (Zhu et al., 2013).
(B and C) (B) Agelasine D oxime functioning as an anti-fouling compound (Hertiani et al., 2010) and **(C)** HI-6 that has the potential to remediate nerve agent poisoning as it is able to reverse acetylcholinesterase inhibition caused by intoxicating organophosphates (Kuca et al., 2005). Both are examples of complex oxime structures used in our society. The oxime function is marked in red.

other oximes (Yamafuji, 1953; Yamafuji et al., 1958; Omura and Tsutsumi, 1968), which the organism then possessed the ability to convert, e.g., into nitriles, amides, and carboxylic acids with the final reaction resulting in the nitrogen atom of the oxime function being released as ammonia (Kato et al., 2007; Picmanova et al., 2015). An alternative route to incorporation of oximes into general metabolism is their conversion into amines catalyzed by oximases (Omura et al., 1967). Most of these proposed enzyme-catalyzed transformations have been measured using crude or partially purified enzyme extracts from microbial organisms, algae, plants, and animals (Yamafuji, 1953; Omura et al., 1967; Omura and Tsutsumi, 1968). The proposed plant transoximases and oximases need to be studied in much more detail. If their existence is verified, they would appear to contribute to balance and optimize nitrogen utilization in plants. Likewise, enzymes catalyzing conversion of amino acids into oximes in microorganisms remain to be identified and characterized (Kato et al., 2007). Hypothetically, the reaction might initially have emerged as a route to remove toxic oxygen in the transition from an anoxic biosphere to an oxygenic biosphere.

The initial formation of oximes in plants is most likely to have followed the evolution of CYP79 family enzymes. The CYP79s catalyzing the conversion of amino acids into oximes in plants, e.g., in the biosynthesis of cyanogenic glucosides in gymnosperms and angiosperms, are predicted to have evolved 330 million years ago (Luck et al., 2017). Ferns—one of the earliest land plants—also produce cyanogenic glucosides but do not have CYPs belonging to the CYP79 family (Nelson and Werck-Reichhart, 2011). It is not known whether an ancestral form of a CYP that gave rise to the CYP79 family is present and catalyzing the oxime-forming reaction in ferns or whether oxime production in ferns is catalyzed by entirely different types of enzymes or from aldehydes by a transoximase activity. In plants, the further conversion of the E-oxime into a cyanohydrin is catalyzed by a CYP71 or CYP736 family enzyme (Jørgensen et al., 2011; Takos et al., 2011) and involves an initial rearrangement reaction of the E-oxime into a Z-oxime followed by a dehydration reaction and a final C-hydroxylation. The former two reactions are not typical P450-catalyzed reactions and might represent the survival of a traditional P450-catalyzed reaction from the pre-oxygenic era (Kahn et al., 1999). In the pre-oxygenic era P450s may have served as scavengers of toxic oxygen.

To date, oximes have been identified widely across the kingdoms of life, with an extensive diversity in structure and functionality. In bacteria, this may be exemplified by the presence of isobutyraldehyde *O*-methyloxime produced by, e.g., *Alcaligenes* and *Pseudomonas* species by the action of an aldoxime *O*-methyltransferase catalyzing the final step (Harper and Nelson, 1982; Harper and Kennedy, 1985). In fungi, an example is the oxime functional group of caerulomycin A (Figure 7A) originally isolated from *Streptomyces caeruleus*. Caerulomycin A formation is catalyzed by a flavin-dependent two-component monooxygenase (Zhu et al., 2013). In mosses, oxime formation may be exemplified by the alkaloid oxime lycoposerramine-B in the club moss (*L. serratum*) (Katakawa et al., 2005), and in marine sponges, the formation of diterpene alkaloid oxime derivatives (Hertiani et al., 2010) and structurally complex bromotyrosine-derived alkaloid oximes is observed (Qi and Ma, 2017). In insects, oximes are also observed to be involved in defense, e.g., by the production of phenylacetaldoxime in millipedes (*Harpaphe haydeniana*), as an intermediate in the synthesis of mandelonitrile stored in the cells, and following dissociation secreted as hydrogen cyanide and benzaldehyde (Duffey et al., 1974). Oxime formation is also found in mammalians, here exemplified by the presence of phenylacetaldoxime and 3-methylthiopropanal oxime in the sternal gland of the marsupial male koala (Salamon and Davies, 1998), and in testosterone-treated guinea pigs by the excretion of phenylacetaldehyde oxime in the urine (Smith et al., 1977). Vertebrates and insects may also sequester oximes present in their feed for use in their own defense, as illustrated by amphibians depositing alkaloid oximes from ingested millipedes in their skin (Daly, 1995). Overall, the occurrence of this type of oximes with high structural complexity across different organisms is widespread but has not been studied systematically in plants.

OXIMES IN THE DAILY LIFE OF HUMAN SOCIETY

Chemically synthesized oximes are used in all sectors of our society. A huge body of literature is available on the chemical synthesis of specific, often structurally complex oximes and their applications. Especially oxime ethers have been reported to possess interesting properties, e.g., as plant growth regulators preventing ethylene formation by inhibiting

1-aminocyclopropane-1-carbocylic acid synthase (Kirchner et al., 1992). This biological property has been exploited to promote shoot formation in silktree (*Albizzia julibrissin*) *in vitro* tissue cultures or to delay senescence and extend shelf-life of cut carnation (*Dianthus caryophyllus*) flowers (Grossmann et al., 1991; Kirchner et al., 1993; Sankhla et al., 1995; Zeng et al., 2012).

Oximes with diverse structures have found multiple uses in the agro-sector as plant protectants and in weed management, exhibiting strong insecticidal, fungicidal, and herbicidal activity (Drumm et al., 1995; Song et al., 2005; Koo et al., 2006). This can be exemplified by oxime derivatives of gossypol that exhibit anti-viral, insecticidal, and fungicidal activity (Li et al., 2016). Gossypol is a metabolite found in cotton (*Gossypium* sp.) plants. Another example is biflorin, an o-naphthoquinone produced by *Capraria biflora* that has been shown to possess anti-microbial activities. However, the biflorin-derived methyl and ethyl oximes show improved anti-bacterial potential compared with biflorin (Souza et al., 2016). Moreover, penta-1,4-diene-3-one oxime ethers show good anti-viral activities, e.g., toward tobacco mosaic virus, and could be promising templates for the design of other related compounds to combat viral diseases in plants (Wang et al., 2017). In general, compounds harboring a pyrazole oxime unit are effective plant protectants and also possess anti-tumor effects (Dai et al., 2016). Also, strobilurin derivatives incorporating an indole-substituted oxime ether are strong fungicides (Xie et al., 2015). Chemically synthesized oxime ethers are obviously subject to a great amount of research but their presence in plants has not been investigated systematically.

In the maritime industry, alkaloid oxime derivatives from marine sponges (*Agelas linnaei*) (Figure 7B) (Hertiani et al., 2010) and structurally complex bromotyrosine-derived alkaloid oximes (Qi and Ma, 2017) are used as biologically benign anti-fouling compounds. In the maritime industry, oximes immobilized on carbon spheres are used to absorb uranyl ions from contaminated sea waters (Zheng et al., 2017).

In the health sector, oximes such as HI-6 (Figure 7C) have in several cases been proved able to reverse acetylcholinesterase inhibition caused by intoxicating organophosphates. These oximes are therefore used in treatment of nerve agent poisoning (Dawson, 1994; Kuca et al., 2005; Kovarik et al., 2008; Singh et al., 2015). Oximes of aliphatic aldehydes were found to inhibit the activity of horse liver and yeast alcohol dehydrogenase (Sigman et al., 1982).

CONCLUDING REMARKS AND FUTURE PERSPECTIVES

Oximes currently known from plants are, except for a few exceptions, amino acid derived and their structures thus reasonably simple (see Table 1). The exceptions include methoxyphenyl oxime (methyl *N*-hydroxybenzimidate), lycoposerramine-B, and citaldoxime. However, to our knowledge no systematic studies have been carried out to investigate the possible occurrence of structurally more complex oximes derived, e.g., from a range of aldehydes by the action of putative enzymes with transoximase activity. Oximes formed in this way may indeed have been observed as present by non-targeted metabolite profiling but not reported because they were considered artifacts of the experimental procedure. Enzymes with transoximase activity have been reported but these early investigations need to be revisited using modern techniques. Reports of oximases catalyzing the conversion of oximes into amines also need verification. A number of O-methylated oximes have been reported to be formed in plants following herbivory. In all cases reported, they represent methylethers of oximes derived from amino acids. Some methylated oximes possess enhanced bioactivity compared with the free oximes. We expect that a systematic search for the presence of O-methylated oximes in plants would offer very interesting results. If present, they are likely to be highly active fungicides. In the cyanogenic glucoside-producing plants, fungal attack and an associated burst of ROS may inactivate the labile CYP71 enzyme that would otherwise have catalyzed conversion of the E-oxime into a cyanohydrin. This would disrupt metabolon formation and render the E-oxime accessible to O-methylation by a methyl-transferase.

Studies of plant general and specialized metabolism have identified oximes as key intermediates in a number of biosynthetic pathways. Interestingly, the oxime intermediate may constitute a metabolic point of bifurcation toward general or specialized metabolism. This identifies oximes as chameleons in plant metabolism. In spite of their involvement in biosynthetic pathways characterized by a high carbon flux such as those resulting in formation of cyanogenic glucosides and glucosinolates, the level of free oxime intermediate observed is minute. The lability and high bioactivity of oximes may require rapid further metabolism or metabolic containment, e.g., via metabolon formation. Like a chameleon, the presence of minute amounts of oximes in a biological sample is therefore easily overlooked unless it is a direct focus of the study.

As discussed in this review, the direct biosynthetic route to oxime formation from amino acids is catalyzed by CYP79s. Genes encoding enzymes of the CYP79 family are present in all eudicots and non-eudicot angiosperms. All flowering plants thus have the CYP79 blueprint to, theoretically, produce oximes. It is important to identify the role of these CYP79s, and we speculate they may be involved in producing auxin or compounds released as volatiles. When liberated as volatiles, the oximes have been shown to attract pollinators. In cyanogenic glucoside synthesis, the CYP79 has been shown to catalyze the specific formation of the E-geometrical isomer of the oxime: E-oximes are strong fungicides. CYP79s involved in volatile formation appear to catalyze a mixture of the E- and Z-geometrical forms. This is certainly possible but could also reflect a purely chemical conversion of the E-to the Z-geometrical form subsequent to the enzyme-catalyzed reaction. In contrast to E-oximes, Z-oximes are easily metabolized by most fungi and bacteria and used as a source of reduced nitrogen. This process involves conversion of the Z-oxime into the corresponding nitrile, amide, and carboxylic acid with a concomitant release of ammonia. The same endogenous turnover process has been demonstrated to operate in plants producing cyanogenic glucosides. The highly interesting enzymes catalyzing this process have been subject to detailed characterization in bacteria and fungi. In plants, only the heteromeric nitrilase involved has been identified and characterized. We hope by this review to inspire more researchers to embark

into the elucidation of the wonderful biochemical world regarding the formation and functional roles of oximes.

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AUTHOR CONTRIBUTIONS

All authors contributed with ideas and shape of the manuscript outline. M.S. prepared a first draft and the table and figures. All authors contributed to the subsequent writing phases with revisions and approved the final manuscript.

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